REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)

Substance Name: Lead and compounds (inorganic)
CASRN: 7439-92-1

Status: Message

Note: A great deal of information on the health effects of lead has been obtained through decades of medical observation and scientific research. This information has been assessed in the development of air and water quality criteria by the Agency's Office of Health and Environmental Assessment (OHEA) in support of regulatory decision-making by the Office of Air Quality Planning and Standards (OAQPS) and by the Office of Drinking Water (ODW). By comparison to most other environmental toxicants, the degree of uncertainty about the health effects of lead is quite low. It appears that some of these effects, particularly changes in the levels of certain blood enzymes and in aspects of children's neurobehavioral development, may occur at blood lead levels so low as to be essentially without a threshold. The Agency's RfD Work Group discussed inorganic lead (and lead compounds) at two meetings (07/08/85 and 07/22/85) and considered it inappropriate to develop an RfD for inorganic lead. For additional information, interested parties are referred to the 1986 Air Quality Criteria for Lead (EPA-600/8-83/028a-dF) and its 1990 Supplement (EPA/600/8-89/049F) or the following Agency scientists:

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REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)

Substance Name: Polychlorinated biphenyls (PCBs)
CASRN: 1336-36-3

Status: Message

Note: Please check the following individual aroclor files for RfD assessments: Aroclor 1016, Aroclor 1248, Aroclor 1254, Aroclor 1260.

REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)

Substance Name: Aroclor 1016
CASRN: 12674-11-2

The Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis, but may not exist for other toxic effects such as carcinogenicity. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Oral RfD Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of compounds which are also carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in the Carcinogenicity Assessment Section of this file when a review of that evaluation is completed.

RfD ASSESSMENT SUMMARY TABLE

Crit. Dose: 0.007 mg/kg-day [Study 1 NOAEL(adj)]
UF: 100 MF: 1 RfD: 7E-5 mg/kg-day Confidence: Medium

Crit Effect: (1) Reduced birth weights

	NOAEL (Study 1)	LOAEL (Study 1)
Reported	0.25 ppm in feed	1 ppm in feed
ADJ	0.007 mg/kg-day	0.028 mg/kg-day
Study Type	Monkey Reproductive Bioassay	Monkey Reproductive Bioassay
Reference	Barsotti and van Miller, 1984; Levin et al., 1988; Schantz et	Barsotti and van Miller, 1984; Levin et al., 1988; Schantz et

1) Barsotti and van Miller, 1984; Levin et al., 1988; Schantz et al., 1989, 1991
Monkey Reproductive Bioassay

Critical Effect: Reduced birth weights

Defined Dose Levels:

NOAEL=	0.25 ppm in feed
NOAEL(ADJ)=	0.007 mg/kg-day
LOAEL=	1 ppm in feed
LOAEL(ADJ)=	0.028 mg/kg-day

Conversion Factors: Dams received a total average intake of 4.52 mg/kg (0.25 ppm) or 18.41 mg/kg (1 ppm) throughout the 21.8-month (654 days) dosing period. These doses are equivalent to 0.007 mg/kg-day and 0.028 mg/kg-day for the identified NOAEL and LOAEL, respectively.

REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)

DISCUSSION OF PRINCIPAL AND SUPPORTING STUDIES

Barsotti, D.A. and J.P. van Miller. 1984. Accumulation of a commercial polychlorinated biphenyl mixture (Aroclor 1016) in adult rhesus monkeys and their nursing infants. Toxicology. 30: 31-44.

Levin, E.D., S.L. Schantz and R.E Bowman. 1988. Delayed spatial alternation deficits resulting from perinatal PCB exposure in monkeys. Arch. Toxicol. 62: 267-273.

Schantz, S.L., E.D. Levin, R.E. Bowman et al. 1989. Effects of perinatal PCB exposure on discrimination-reversal learning in monkeys. Neurotoxicol. Teratol. 11: 243-250.

Schantz, S.L., E.D. Levin and R.E. Bowman. 1991. Long-term neurobehavioral effects of perinatal polychlorinated biphenyl (PCB) exposure in monkeys. Environ. Toxicol. Chem. 10: 747-756.

These are a series of reports that evaluated perinatal toxicity and long-term neurobehavioral effects of Aroclor 1016 in the same groups of infant monkeys. Aroclor 1016 is a commercial mixture of polyclorinated biphenyls (PCBs) devoid of chlorinated dibenzofurans (Barsotti and van Miller, 1984). Analysis of the commercial feed used for this study revealed contamination with congeners specific for Aroclor 1248, present in the parts per billion range. These congeners were present in the control as well as test diets. Aroclor 1016 was administered to groups of 8 adult female rhesus monkeys via diet in concentrations of 0, 0.25 or 1.0 ppm for approximately 22 months. Based on a reported total Aroclor intake of 4.52 and 18.41 mg/kg over the 22-month exposure period (Schantz et al., 1989, 1991), the low- and high-doses are estimated to be 0.007 and 0.028 mg/kg-day, respectively. Exposure began 7 months prior to breeding and continued until offspring were weaned at age 4 months. No exposure-related effects on maternal food intake, general appearance, hematology, serum chemistry (SGPT, lipid, and cholesterol analyses) or number of breedings were observed (Barsotti and van Miller, 1984). All monkeys had uncomplicated pregnancies, carried their infants to term and delivered viable offspring. Teratologic examinations were not performed. Mean birth weights of the infants in the control, 0.007 and 0.028 mg/kg-day dose groups were 521 g, 491 g and 442 g, respectively (Barsotti and van Miller, 1984). The decrease in birth weight in the high-dose group was significantly ($p<0.01$) lower than in controls. Further statistical analysis of the infant birth weight data by the Agency indicated that gestation length did not

significantly affect birth weight and the distribution of male and female infants in the various dose groups could not account for the difference in birth weights among the dose groups. Agency reanalysis of the data confirmed the significant decrease in body weight for the high-dose infants, although slightly different average values were obtained. Males that had sired some infants were exposed to Aroclor 1248, so the birth weight data were also analyzed excluding these infants. The results for this adjusted data indicated that control infants weighed 528 g, low-dose infants weighed 486 g, and high-dose infants weighed 421 g. Even with this adjustment there was still a significant difference ($p<0.01$) in birth weight for the high-dose group when compared with controls. No significant differences between treatment and control groups were detected in neonatal head circumference or crown-to-rump measurements. Both exposure groups showed consistent weight gains, but infant weights in the high-dose group were still lower (864 g) at weaning, although

not significantly different from the controls (896 g). Hyperpigmentation was present at birth in the low- and high-dose infants but did not persist once dosing was stopped. This clinical change was determined not to be a critical adverse effect. The concentration of Aroclor 1016 in breast milk was higher than the maternal dose. No exposure-related hematologic effects were observed in the infants during the nursing period (Barsotti and van Miller, 1984). One of the offspring in the high-dose group went into shock and died on the day following weaning for unknown reasons (Schantz et al., 1989, 1991).

Behavioral testing of the infant monkeys was first performed at age 14 months and no overt signs of PCB toxicity were observed (Schantz et al., 1989, 1991). Two-choice discrimination-reversal learning was assessed using simple left-right spatial position, color and shape discrimination problems, with and without irrelevant color and shape cues. One of the offspring in the low-dose group stopped responding early in testing for an unknown reason and could not be induced to resume; therefore, test results were obtained using 6, 7 and 6 infants in the control, low- and high-dose groups, respectively. The offspring in the high-dose (0.028 mg/kg-day) group were significantly ($p<0.05$) impaired in their ability to learn the spatial position discrimination problem (i.e., achieved 9 correct choices in 10 trials), requiring more than 2.5 times as many trials as their age-matched controls. There were no significant learning differences between these groups on this problem during overtraining (ability to achieve greater than or equal to 90% correct choices in two consecutive daily sessions) or position reversals. The only other exposure-related effect was significantly facilitated learning ability ($p<0.05$) on the shape discrimination problem at 0.028 mg/kg-day.

Performance on delayed spatial alternation (a spatial learning and memory task) was assessed in the offspring monkeys at age 4-6 years (Levin et al., 1988; Schantz et al., 1991). The two Aroclor-exposed groups were not significantly different from controls ($p<0.05$) in test performance. However, the exposed groups did significantly ($p<0.05$) differ from each other. The difference between the two exposed groups was due to a combination of facilitated performance at the low-dose (0.007 mg/kg-day) and impaired performance at the high-dose (0.028 mg/kg-day). Although these data are insufficient for establishing an exposure-effect relation due to the lack of difference between exposed and control groups, the investigators suggested that the performance deficit at 0.028 mg/kg-day may have been exposure-related. The investigators noticed that a paradoxical biphasic effect occurred on the same test when comparing low-dose and high-dose infants. This same effect has been observed for lead-exposed monkeys.

To summarize the above, adult monkeys that ingested 0.007 or 0.028 mg/kg-day doses of Aroclor 1016 for approximately 22 months showed no evidence of overt toxicity. Effects occurring in the offspring of these monkeys consisted of hairline hyperpigmentation at greater than or equal to 0.007 mg/kg-day, and decreased birth weight and possible neurologic impairment at 0.028 mg/kg-day. Based on the reduced birth weights of prenatally-exposed monkeys, the 0.007 mg/kg-day dose is the NOAEL and the 0.028 mg/kg-day dose is a LOAEL in monkeys.

The results of the neurobehavioral tests in the monkey offspring at 14 months and 4-6 years of age indicate adverse learning deficits at the 0.028 mg/kg-day maternal dose. Evaluation of these data is complicated by possible inconsistencies in the outcome of both the discrimination-reversal learning tests (learning was impaired and facilitated on different problems) and the

delayed spatial alternation test (performance significantly differed between the two exposed groups, but not between either test group and the control). However, there is evidence suggesting that deficits in discrimination-reversal learning and delayed spatial alternation are related to decreased brain dopamine (Schantz et al., 1991), which has been observed in monkeys orally exposed to Aroclor 1016 (Seegal et al., 1990, 1991). Behavioral dysfunctions, including deficits in visual recognition and short-term memory, also have been observed in infants of human mothers who consumed fish contaminated with PCB mixtures of unknown composition (Fein et al., 1984a,b; Jacobsen et al., 1985, 1990; Gladen et al., 1988).

UNCERTAINTY AND MODIFYING FACTORS

UNCERTAINTY FACTORS:

A 3-fold factor is applied to account for sensitive individuals. The results of these studies, as well as data for human exposure to PCBs, indicate that infants exposed transplacentally represent a sensitive subpopulation. A factor of 3 is applied for extrapolation from rhesus monkeys to human. A full 10-fold factor for interspecies extrapolation is not considered necessary because of similarities in toxic responses and metabolism of PCBs between monkeys and humans and the general physiologic similarity between these species. In addition, the rhesus monkey data are predictive of other changes noted in human studies such as chloracne, hepatic changes, and effects on reproductive function. A factor of 3 is applied because of limitations in the data base. Despite the extensive amount of animal laboratory data and human epidemiologic information regarding PCBs, the issue of male reproductive effects is not directly addressed and two-generation reproductive studies are not available. As the study duration was considered as somewhat greater than subchronic, but less than chronic, a partial factor of 3 is used to account for extrapolation from a subchronic exposure to a chronic RfD.

MODIFYING FACTORS:

None

ADDITIONAL COMMENTS / STUDIES

Male pig-tailed macaques [Macaca nemistrina], (number not reported, age 3-7 years, 5-9 kg initial body weight) were administered Aroclor 1016 dissolved in

corn oil on bread in doses of 0, 0.8, 1.6 or 3.2 mg/kg-day for 20 weeks (Seegal et al., 1991). There were no overt signs of intoxication or exposure-related effects on body weight gain. Neurochemical analyses of various regions of the brain were performed following termination of exposure. Dose-related decreased concentrations of dopamine were observed in the caudate nucleus, putamen, substantia nigra, and hypothalamus, but not in the globus pallidus or hippocampus. There were no exposure-related changes in concentrations of norepinephrine, epinephrine, or serotonin. Other neurologic endpoints were not evaluated.

Subchronic oral studies of Aroclor 1016 have been performed in species other than monkeys. These species were tested at doses higher than the 0.007 and 0.028 mg/kg-day doses fed to monkeys in the principal studies.

REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)

Substance Name: Cadmium
CASRN: 7440-43-9

The Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis, but may not exist for other toxic effects such as carcinogenicity. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Oral RfD Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of compounds which are also carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in the Carcinogenicity Assessment Section of this file when a review of that evaluation is completed.

Note: Note: Two Rfds for cadmium have been derived, one for drinking water (given in the summary table) and one for food. The Rfd for dietary exposure is 1E-3 mg/kg-day.

RfD ASSESSMENT SUMMARY TABLE

Crit. Dose: 0.005 mg/kg-day [Study 1 NOAEL]
UF: 10 MF: 1 RfD: 5E-4 mg/kg-day Confidence: High

Crit Effect: (1) Significant proteinuria

	NOAEL (Study 1)	LOAEL (Study 1)
Reported	0.005 mg/kg-day (water); 0.01 mg/kg-day (food)	none
ADJ	0.005 mg/kg-day	mg/kg-day
Study Type	Human studies involving chronic exposures	Human studies involving chronic exposures
Reference	U.S. EPA, 1985	U.S. EPA, 1985

1) U.S. EPA, 1985

Human studies involving chronic exposures

Critical Effect: Significant proteinuria

Defined Dose Levels:
NOAEL= 0.005 mg/kg-day (water); 0.01 mg/kg-day (food)
NOAEL(ADJ)= 0.005 mg/kg-day
LOAEL= none
LOAEL(ADJ)=

Conversion Factors: See text for discussion

REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)

DISCUSSION OF PRINCIPAL AND SUPPORTING STUDIES

U.S. EPA. 1985. Drinking Water Criteria Document on Cadmium. Office of Drinking Water, Washington, DC. (Final draft)

A concentration of 200 ug cadmium (Cd)/gm wet human renal cortex is the highest renal level not associated with significant proteinuria (U.S. EPA, 1985). A toxicokinetic model is available to determine the level of chronic human oral exposure (NOAEL) which results in 200 ug Cd/gm wet human renal cortex; the model assumes that 0.01% day of the Cd body burden is eliminated per day (U.S. EPA, 1985). Assuming 2.5% absorption of Cd from food or 5% from water, the toxicokinetic model predicts that the NOAEL for chronic Cd exposure is 0.005 and 0.01 mg Cd/kg/day from water and food, respectively (i.e., levels which would result in 200 ug Cd/gm wet weight human renal cortex). Thus, based on an estimated NOAEL of 0.005 mg Cd/kg/day for Cd in drinking water and an UF of 10, an RfD of 0.0005 mg Cd/kg/day (water) was calculated; an equivalent RfD for Cd in food is 0.001 mg Cd/kg/day (see Section VI.A. for references).

UNCERTAINTY AND MODIFYING FACTORS

UNCERTAINTY FACTORS:

This uncertainty factor is used to account for intrahuman variability to the toxicity of this chemical in the absence of specific data on sensitive individuals.

ADDITIONAL COMMENTS / STUDIES

Cd is unusual in relation to most, if not all, of the substances for which an oral RfD has been determined in that a vast quantity of both human and animal toxicity data are available. The RfD is based on the highest level of Cd in the human renal cortex (i.e., the critical level) not associated with significant proteinuria (i.e., the critical effect). A toxicokinetic model has been used to determine the highest level of exposure associated with the lack of a critical effect. Since the fraction of ingested Cd that is absorbed appears to vary with the source (e.g., food vs. drinking water), it is necessary to allow for this difference in absorption when using the toxicokinetic model to determine an RfD.

CONFIDENCE IN THE RfD

Study: Data Base: High RfD: High

The choice of NOAEL does not reflect the information from any single study. Rather, it reflects the data obtained from many studies on the toxicity of cadmium in both humans and animals. These data also permit calculation of pharmacokinetic parameters of cadmium absorption, distribution, metabolism and elimination. All of this information considered together gives high confidence in the data base. High confidence in either RfD follows as well.

EPA DOCUMENTATION AND REVIEW

Source Document: U.S. EPA. 1985. Drinking Water Criteria Document on Cadmium. Office of Drinking Water, Washington, DC. (Final draft)

REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)

Agency Work Group Review: 05/15/86, 08/19/86, 09/17/87, 12/15/87, 01/20/88, 05/25/88

Verification Date: 05/25/88

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REVISION HISTORY

10/89 RfD Data: Oral RfD summary on-line
10/89 RfD Refs: Oral RfD references added
02/94 RfD Contact: Secondary contact changed